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## **Rationale and Design of a Clinical Trial Investigating Tolvaptan Safety and Efficacy in Autosomal Dominant Polycystic Kidney Disease**

Torres, Vicente E ; Devuyst, Olivier ; Chapman, Arlene B ; Gansevoort, Ron T ; Perrone, Ronald D ;  
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## Tolvaptan and Kidney Pain in Patients With Autosomal Dominant Polycystic Kidney Disease: Secondary Analysis From a Randomized Controlled Trial

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### Abstract

**Background**—Kidney pain is a common complication in patients with autosomal dominant polycystic kidney disease (ADPKD), and data from the TEMPO 3:4 trial suggested that tolvaptan, a vasopressin V2 receptor antagonist, may have a positive effect on kidney pain in this patient group. Because pain is difficult to measure, the incidence of kidney pain leading to objective medical interventions was used in the present study to assess pain.

**Study Design**—Secondary analysis from a randomized controlled trial.

**Setting & Participants**—Patients with ADPKD with preserved kidney function.

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\*A full list of the TEMPO 3:4 Investigators is given in the Supplemental Appendix of Torres et al.<sup>5</sup>

### SUPPLEMENTARY MATERIAL

Table S1: Cross-sectional associations of baseline characteristics with kidney pain history in overall population in TEMPO 3:4.

Table S2: Associations of baseline characteristics with first kidney pain events during 3 y follow-up in tolvaptan group.

Table S3: Incidence of patients having first kidney pain event during 3 y follow-up.

Table S4: Cumulative incidence of all kidney pain events during 3 y follow-up according to severity of pain.

Figure S1: Assessment of assumption of proportional hazards for time to first acute kidney pain event.

Note: The supplementary material accompanying this article (<http://dx.doi.org/10.1053/j.ajkd.2016.08.028>) is available at [www.ajkd.org](http://www.ajkd.org)

**Intervention**—Tolvaptan or placebo.

**Outcomes**—Kidney pain events defined by objective medical interventions.

**Measurements**—Kidney pain events were recorded and independently adjudicated. Incidence of a first kidney pain event was assessed overall and categorized into 5 subgroups according to severity.

**Results**—Of 1,445 participating patients (48.4% women; mean age,  $39 \pm 7$  [SD] years; mean estimated glomerular filtration rate,  $81 \pm 22$  mL/min/1.73 m<sup>2</sup>; median total kidney volume, 1,692 [IQR, 750–7,555] mL), 50.9% reported a history of kidney pain at baseline. History of urinary tract infections, kidney stones, or hematuria (all  $P < 0.001$ ) and female sex ( $P < 0.001$ ) were significantly associated with history of kidney pain. Tolvaptan use resulted in a significantly lower incidence of kidney pain events when compared to placebo: 10.1% versus 16.8% ( $P < 0.001$ ), with a risk reduction of 36% (HR, 0.64; 95% CI, 0.48–0.86). The reduction in pain event incidence by tolvaptan was found in all groups irrespective of pain severity and was independent of predisposing factors ( $P$  for interaction  $> 0.05$ ). The effect of tolvaptan was explained at least in part by a decrease in incidence of urinary tract infections, kidney stones, and hematuria when compared to placebo.

**Limitations**—Trial has specific inclusion criteria for total kidney volume and kidney function.

**Conclusions**—Tolvaptan decreased the incidence of kidney pain events independent of patient characteristics predisposing for kidney pain and possibly in part due to reductions in ADPKD-related complications.

## INDEX WORDS

Autosomal dominant polycystic kidney disease (ADPKD); pain; tolvaptan; vasopressin; acute kidney pain event; TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes) 3:4; pain severity; analgesic

Pain is a common complication in patients with autosomal dominant polycystic kidney disease (ADPKD). It is a symptom that is often reported early in the disease course and that sometimes can be severe and difficult to manage and adversely affect a patient's quality of life.<sup>1–3</sup> Acute pain in patients with ADPKD can be caused by cyst hemorrhage, infection, and kidney stones, which are often accompanied by hematuria. When pain is present longer than 4 to 6 weeks, it is typically classified as chronic pain, which has a reported prevalence as high as 60%.<sup>4</sup>

The TEMPO (Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes) 3:4 trial demonstrated the renoprotective effects of tolvaptan treatment in a randomized controlled clinical trial setting.<sup>5</sup> During 3 years' follow-up, tolvaptan, a vasopressin V2 receptor antagonist, reduced the annual rate of growth in total kidney volume (TKV) from 5.5% to 2.8% ( $P < 0.001$ ) and the annual rate of estimated glomerular filtration rate (eGFR) decline from  $-3.70$  to  $-2.72$  mL/min/1.73 m<sup>2</sup> ( $P < 0.001$ ) compared to placebo.<sup>5</sup> This trial also demonstrated a reduction in clinical progression as assessed by its key secondary composite end point through a reduction of ADPKD-related clinical events. This outcome was driven by 2 components of the

composite: time to decline in kidney function and time to clinically significant kidney pain events.<sup>5</sup>

In the present study, we explored this last finding more closely. We characterized what constituted a “clinically significant kidney pain event” by objectively examining the intensity of medical interventions used to define them. We also investigated the association of ADPKD clinical characteristics (such as history of kidney pain, infection, kidney stones, or hematuria at baseline) with the incidence of acute kidney pain events during the 3-year trial. Furthermore, we analyzed the effect of tolvaptan use on incidence of kidney pain events and explored whether new pain events were associated with baseline patient characteristics and the possible mechanisms by which tolvaptan reduced their incidence.

## METHODS

### Study Design and Patients

The present study was performed as a post hoc exploratory analysis of the TEMPO 3:4 trial, a prospective, blinded, randomized, placebo-controlled trial in patients with diagnosed ADPKD (ClinicalTrials.gov study number NCT00428948). Patients were enrolled at 129 sites worldwide during January 2007 to January 2009. Inclusion criteria were age 18 to 50 years with a diagnosis of ADPKD, TKV measured by magnetic resonance imaging  $\geq 750$  mL, and creatinine clearance estimated by the Cockcroft-Gault formula  $\geq 60$  mL/min. Exclusion criteria included, among others, concomitant illnesses likely to confound end point assessments, such as diabetes mellitus, and prior kidney surgery. The institutional review board or ethics committee at each site approved the protocol. Written informed consent was obtained from all participants. Details of the study protocol<sup>6</sup> and the primary study results<sup>5</sup> have been published previously. This report has been prepared in accordance with the CONSORT (Consolidated Standards of Reporting Trials) 2010 Statement.<sup>7</sup>

### Study Treatment

Patients were randomly assigned to receive tolvaptan or placebo (2:1). Tolvaptan dosing was started at 45 mg AM/15 mg PM (daily split dose) and increased weekly to 60/30 mg and 90/30 mg if tolerated. Patients remained on the highest tolerated dose for 36 months.

### Study Assessments and Definitions

Evaluations were performed at baseline, every 4 months during treatment, and twice for 2 to 6 weeks after completion of treatment at 36 months and included interviews, examinations, vital sign measurements, and blood and trough spot morning urine samples. TKV was assessed using standardized kidney magnetic resonance imaging at baseline and months 12, 24, and 36 or at early withdrawal. In addition, height-adjusted TKV was calculated as TKV in milliliters divided by height in meters. Serum creatinine level was reported to 2 decimal points and used to estimate GFR (applying the CKD-EPI [Chronic Kidney Disease Epidemiology Collaboration] equation).<sup>8</sup>

At baseline, a standardized interview was performed to gather information about demographic characteristics and medical history, including information for prior kidney

pain. Incidence of acute kidney pain during follow-up was a component of the composite secondary efficacy end point, which assessed kidney pain events requiring medical intervention and that required documentation of clinical signs and symptoms that pain was kidney related (ie, flank tenderness or evidence of cystic expansion or hemorrhage). The investigator's clinical judgment was required to arbitrate whether the level of pain met the definition of end point, which required clinically significant kidney pain necessitating pharmacologic treatment or invasive intervention. Pain was a priori categorized according to the intensity of intervention into 5 groups: mild, prescription of acetaminophen; moderate, prescription of other non-narcotic analgesics; moderately severe, prescription of non-narcotic analgesic and limitation in physical activity; severe, prescription of narcotic analgesics; most severe, need for hospitalization and/or invasive intervention. Events were assessed by an independent adjudication committee blinded for treatment allocation. Finally, the incidence of urinary tract infection, kidney stones, and hematuria was assessed as a composite score and separately. Of note, the initial TEMPO 3:4 trial publication provided data for these events only when reported as (serious) adverse events, whereas in the present study, all clinically significant pain-related adverse events are taken into account.

### Study Outcomes

The primary end point in this study was the effect of tolvaptan use on incidence of acute kidney pain events compared to placebo. Second, we investigated: (1) the association of ADPKD clinical characteristics (such as history of kidney pain, infection, kidney stones, or hematuria at baseline) with the incidence of acute kidney pain events during the 3-year trial, (2) whether new acute kidney pain events were associated with baseline patient characteristics, and (3) the possible mechanisms by which tolvaptan reduced their incidence.

### Statistical Analyses

Baseline characteristics were calculated for participants with and without a history of kidney pain separately. Normally distributed variables are expressed as mean  $\pm$  standard deviation, whereas non-normally distributed variables are given as median (interquartile range [IQR]). Differences in baseline characteristics between patients with and without a history of kidney pain were calculated with  $\chi^2$  test for categorical data, and for continuous data, with *t* test or Mann-Whitney *U* test in case of non-normally distributed data. To investigate whether baseline patient characteristics correlated with a history of kidney pain, univariate and multivariate logistic regression analyses were performed. The multivariate logistic analyses were subsequently adjusted for sex, age, height-adjusted TKV, and eGFR to investigate the impact of patient characteristics that predispose for kidney pain events that are not associated with disease severity. TKV, height-adjusted TKV, and albumin-creatinine ratio were log<sub>2</sub>-transformed to fulfill the requirement of normal distribution of the residuals for regression analysis.

In the placebo and tolvaptan groups, the overall incidence of a first acute kidney pain event during the 3-year trial was assessed in the intention-to-treat population, and the incidence of acute kidney pain events was subdivided in 5 categories named by pain severity and defined by the medical intervention used to treat the event. Cox proportional hazards regression analyses were performed to investigate whether baseline characteristics associated with the

first acute kidney pain event during the trial, with censoring of patients lost to follow-up or stopping study medication. First, unadjusted hazard ratios (HRs) with 95% confidence intervals were calculated. Second, we calculated multivariate-adjusted HRs, which were adjusted for sex, age, height-adjusted TKV, and eGFR to investigate the impact of patient characteristics that predispose for acute kidney pain events that are not associated with disease severity. The number needed to treat to prevent 1 acute kidney pain event was calculated based on the cumulative event proportions. In addition, we investigated the effect of tolvaptan on incidence of acute kidney pain events in the overall TEMPO 3:4 trial population and in subgroups according to baseline characteristics, and *P* for interaction by subgroup was calculated. Last, the effect of tolvaptan on renal complications known to cause pain was investigated.

Two sensitivity analyses were performed. First, the effect of tolvaptan on incidence of acute kidney pain events was investigated as time to first occurrence of each specific category of intervention/pain severity instead of as cumulative incidence. Second, the effect of tolvaptan was investigated including multiple acute kidney pain events per patient. All analyses were performed with SAS, version 9.2 statistical software (SAS Institute Inc), and 2-sided *P* < 0.05 was considered to indicate statistical significance.

## RESULTS

### Baseline Characteristics

A total of 1,445 patients with ADPKD were enrolled in the TEMPO 3:4 trial (Fig 1). Mean age was  $39 \pm 7$  years, and 48.4% were women (Table 1). By protocol, patients had preserved kidney function, with mean eGFR of  $81 \pm 22$  mL/min/1.73 m<sup>2</sup> and median TKV of 1,692 (IQR, 750–7,555) mL. At baseline, 50.9% of participants reported having a history of kidney pain. Patient characteristics were stratified according to those with or without a history of kidney pain (Table 1). A history of urinary tract infection, kidney stones, or hematuria was associated with having a history of kidney pain. Other significant associations included female sex, smaller body size, and lower urine osmolality, although for the last 2 variables, the absolute difference between patients with and without a history of kidney pain was small and likely not clinically relevant. Each of these characteristics remained significant when adjusted for sex, age, height-adjusted TKV, and eGFR (Table S1, available as online supplementary material). No associations were found for history of kidney pain and eGFR, TKV, or height-adjusted TKV. Of the 1,445 participating patients, 484 were randomly assigned to placebo, and 961, to tolvaptan, of whom 49.4% and 51.6% had a history of kidney pain, respectively (*P* = 0.4). No significant differences in patient characteristics were observed between treatment groups when comparing participants with or without a history of pain.

### Kidney Pain Events Over 3 Years in Placebo Group

In the placebo group, 16.7% of patients had an episode of kidney pain during the 3-year trial. A history of urinary tract infection, kidney stones, hematuria, or kidney pain and female sex tended to be associated with incident kidney pain events (Table 2). After adjusting for age, sex, height-adjusted TKV, and eGFR, these factors were significantly

associated with kidney pain events during the study, except for a history of urinary tract infection (Table 2). No association was found between baseline TKV, height-adjusted TKV, or eGFR with kidney pain events during follow-up; neither crude analysis nor analysis after multivariate adjustment for covariates.

### Effect of Tolvaptan on Incidence of Kidney Pain Events

In contrast to the 16.7% incidence reported for patients in the placebo group, 10.1% of the tolvaptan group had clinically significant kidney pain during the 3-year trial. Identified risk factors for acute kidney pain events in the placebo group, for example, history of kidney stones, hematuria, or kidney pain and female sex, tended also to be associated with incident kidney pain events in the tolvaptan group (Table S2).

Tolvaptan use was associated with a significantly lower incidence of first kidney pain events when compared to placebo ( $P < 0.001$ ), with a risk reduction of 36% (HR, 0.64; 95% confidence interval, 0.48–0.86; Table 3). The difference in cumulative incidence of patients having a kidney pain event between the tolvaptan and placebo groups increased over time (Fig 2). We analyzed the effects of tolvaptan on the incidence of kidney pain events among various subgroups based on specific baseline characteristics (Fig 3). No interactions were found between the effect of tolvaptan on kidney pain and patient characteristics of disease severity, characteristics predisposing for worse renal prognosis, or characteristics predisposing for kidney pain ( $P$  for interaction all nonsignificant). When pain was defined more strictly, similar efficacy of tolvaptan was noted (Table 3). The number needed to treat to prevent 1 pain event ranged from 35 patients when taking any pain event into account (prescription of acetaminophen or worse) to 384 patients when taking only the most severe pain category into account (hospitalization or invasive intervention; Table 3).

Last, we investigated whether the mechanism of tolvaptan in reducing kidney pain events could be elucidated. Patients with ADPKD having an acute kidney pain event had a similar TKV growth rate compared with patients with ADPKD who did not have such an event. This was the case for patients in the placebo group and those in the tolvaptan group (Table 4). The significant reduction in number of participants having reported kidney pain was matched by similar reductions in the incidence of renal complications likely to cause such pain in ADPKD, such as urinary tract infections and kidney stones, and bouts of macroscopic hematuria that can be detected in patients having cyst ruptures and bleeds (infections, 11.1% vs 15.3% [ $P = 0.02$ ]; kidney stones, 2.2% vs 3.5% [ $P < 0.001$ ]; hematuria, 8.0% vs 14.3% [ $P < 0.001$ ]; any of the 3 aforementioned, 18.9% vs 28.7% [ $P < 0.001$ ]). Irrespective of treatment arm, patients with kidney pain events had a higher incidence of these disease-related complications than those not having pain events.

### Sensitivity Analyses

When pain events were analyzed by subgroup of pain severity instead of as cumulative incidence, risk reduction was observed for tolvaptan across all subgroups. Of note, relative risk reductions did not reach formal statistical significance in all subgroups, likely due to the small number of patients per pain category (Table S3). Sensitivity analysis focused on



multiple-event analyses yielded essentially the same result as the primary time-to-first-event analysis (Table S4).

## DISCUSSION

Our study had a cross-sectional and a longitudinal part. In the cross-sectional analysis of baseline data of the TEMPO 3:4 trial, history of kidney pain was observed in 50.9% of participants. Acute kidney pain events in patients with ADPKD are often caused by urologic complications such as urinary tract infections, kidney stones, and cyst bleeding and rupture. The latter 2 are clinically diagnosed by bouts of macroscopic hemorrhage.<sup>1,2,9</sup> In support of this, we found independent associations between history of kidney pain and history of urinary tract infection, kidney stones, and hematuria. Three prior studies have investigated the prevalence of pain in patients with ADPKD in a cross-sectional setting.<sup>10–12</sup> The largest of these studies was performed by Miskulin et al<sup>10</sup> using baseline data from 1,043 patients with ADPKD participating in the HALT–Polycystic Kidney Disease (PKD) studies. The authors described that pain is an early symptom in the course of ADPKD.<sup>10</sup> The percentage of participants with a history of pain events in HALT-PKD was similar to the percentage of participants in the TEMPO 3:4 trial.<sup>5,10</sup> Furthermore, they found that pain prevalence was inversely correlated with eGFR, but only in patients at lower eGFRs ( $<45$  mL/min/1.73 m<sup>2</sup>).<sup>10</sup> In our study, we did not find such an association, which may be explained because TEMPO 3:4 enrolled patients with relatively preserved kidney function (estimated creatinine clearance  $> 60$  mL/min).<sup>5</sup> In the other 2 studies (involving 219 and 152 patients with ADPKD, respectively), pain was assessed in patients across a broad range of kidney function, including patients on dialysis therapy.<sup>11,12</sup> These studies found that pain was positively correlated with the physical component score of health-related quality-of-life questionnaires, but they did not identify potential risk factors for kidney pain. We found that female sex was significantly associated with history of kidney pain, even when adjusted for height, age, and disease severity. To our knowledge, no other study has specifically reported this association. However, the study by Miskulin et al<sup>10</sup> shows that a history of pain was also reported more by female compared with male patients with ADPKD. A history of back pain, for instance, was reported by 56.8% versus 45.1%, respectively.<sup>10</sup> Medical and invasive treatments for pain were also more frequent in female patients. Whether this sex difference is specific for ADPKD is not clear. Several reviews have concluded, for instance, that in the general population, pain is more frequently reported by women than by men.<sup>13,14</sup> It has been suggested that an interaction of biological (eg, sex hormones), psychological (eg, coping strategies), and sociocultural (eg, femininity) factors may contribute to this sex difference.<sup>13</sup>

In the longitudinal part of our study, 16.8% of patients in the placebo group reported acute kidney pain events during the 3-year trial. This is the first trial to prospectively investigate the incidence of such events in ADPKD. We found that history of kidney pain, kidney stones, and hematuria and female sex were associated with incident kidney pain. Therefore, our study shows in a cross-sectional and a longitudinal setting that these factors are associated with acute kidney pain.

In ADPKD, it is generally assumed that large kidney volumes play a role in causing pain. Interestingly, in this study, neither TKV nor height-adjusted TKV associated with acute



kidney pain at baseline (Table 1) or during the trial (Table 2). These results are supported by findings in the 539 patients in the study by Miskulin et al<sup>10</sup> for whom magnetic resonance images were available. In these patients, no relationship was found between TKV and pain except in patients with very large kidneys. The authors proposed that cyst number, size, or location may be more important than TKV in causing pain. However, information for these variables was not available in their study and thus needs additional investigation. Others have suggested that the combined volume of the kidneys and liver is the major determinant of ADPKD-related symptoms, including pain.<sup>11,15</sup> However, total liver volumes were not measured in TEMPO 3:4, so we can neither confirm nor reject this hypothesis.

During the trial, 10.1% of the tolvaptan group had events of clinically significant acute kidney pain compared to 16.8% of the placebo group, indicating a relative risk reduction by tolvaptan of 36% (Table 3). This pain incidence-lowering effect was found in all subgroups defined by intervention and was independent of baseline clinical characteristics shown to predispose for kidney pain. We attempted to determine a mechanism for the kidney pain-lowering effect of tolvaptan. It was hypothesized that patients with a lower TKV growth rate would have a lower incidence of kidney pain events because tolvaptan reduced the rate of TKV growth by 49%.<sup>5</sup> However, per-treatment-arm TKV growth rate was similar in patients having and not having a kidney pain event (Table 4). This finding, in combination with the lack of association between TKV and history of kidney pain at baseline (Table 1) and incident pain events during the trial (Table 2), suggests that the effect of tolvaptan on incidence of kidney pain events may not be primarily related to its effect on TKV growth rate.

Another mechanism may be related to a drug-related decrease in the incidence of renal complications that are known to be associated with acute kidney pain events (eg, a reduction in incidence of urinary tract infections, kidney stones, and cyst hemorrhage and ruptures [assessed as bouts of hematuria]). At baseline and during the trial, associations were found between these disease-related complications and history or incidence of kidney pain. Importantly, tolvaptan lowered the incidence of these complications compared to placebo: urinary tract infections, lowered by 27% ( $P = 0.02$ ); kidney stones, lowered by 37% ( $P < 0.001$ ); and hematuria, lowered by 44% ( $P < 0.001$ ; Table 4). In addition, a significantly higher incidence of these complications was observed in patients having versus not having a kidney pain event, irrespective of treatment arm. Tolvaptan-induced polyuria, which can be up to 4 to 6 L per day, might explain the lower incidence of these aforementioned renal complications because increased water intake is associated with lower recurrence of kidney stones and urinary tract infections in the general population.<sup>16</sup> It may be that increasing water intake to such an extent without using tolvaptan could have a similar effect on acute kidney pain events. However, this has never been studied, and data in the literature suggest that it is questionable whether such high spontaneous water intake is feasible during prolonged periods.<sup>17</sup> Our data indicate that the pain-lowering effect of tolvaptan might be mediated at least in part by a reduction in incidence of renal complications known to be associated with kidney pain. Of note, 58.8% of the tolvaptan group who had a kidney pain event did not report one of these complications. This suggests that other yet unidentified mechanisms may play a role. For instance, it might well be that tolvaptan reduces cyst fluid secretion and thereby fluid pressure within cysts, leading to fewer pain events. Another

possible additional mechanism may be the reflex increase in vasopressin concentration that is observed when the V2 receptor is blocked by tolvaptan.<sup>18,19</sup> Vasopressin stimulates the secretion of  $\beta$ -endorphins by the hypothalamus, which could cause a central analgesic effect.<sup>20,21</sup>

The number needed to treat to prevent one acute kidney event is high to prescribe tolvaptan to patients with ADPKD with the sole aim of preventing such acute kidney pain events and should be weighed against the fact that in the TEMPO 3:4 trial, patients who were given tolvaptan had a greater number of adverse events related to aquaresis (ie, polydipsia, polyuria, and nocturia)<sup>5</sup> and that tolvaptan has a potential hepatotoxic effect. The rates of all observed adverse events during the 3-year trial were discussed in more detail in the initial publication.<sup>5</sup> Any potential benefit should of course be weighed against these disadvantages. In our opinion, the primary aim of prescribing tolvaptan for patients with ADPKD therefore remains its renoprotective efficacy. However, the present analyses indicate that when prescribed, there is an additional benefit that may be important, especially for patients with ADPKD with recurrent acute pain events. When considering whether to prescribe this drug, health care providers should carefully inform patients about potential risks and benefits.

There are limitations to our study worth addressing. First, this study was performed as a post hoc analysis of a randomized controlled trial. However, the outcome under study was prespecified per protocol. Second, the TEMPO 3:4 study had specific inclusion criteria for TKV and eGFR that were defined to enrich the patient population to be included for rapid disease progression. This may make extrapolation of our findings to the general ADPKD population difficult. However, neither the incidence of kidney pain events nor the effect of tolvaptan on kidney pain events was associated with baseline TKV or eGFR, suggesting that our results may be valid in the general ADPKD population. Third, the aquaretic response to tolvaptan causes polyuria. This may have caused unblinding in the study, which may have resulted in under- or overestimation of pain reporting. However, we assessed kidney pain events defined by objective criteria (ie, the need for medical intervention), and moreover, events were adjudicated by an independent committee that was blinded for treatment allocation. Therefore, we consider our data to be robust. Last, this study focuses on only acute kidney pain events and did not investigate the effect of tolvaptan on chronic pain in ADPKD, which is beyond the scope of the present study. The main strength of this study is that it was performed in a large population of patients with ADPKD in several countries across the world, making it seemingly the most comprehensive study available that investigates characteristics predisposing for kidney pain events among patients with ADPKD in a cross-sectional setting and the first study addressing this question in a longitudinal setting. Moreover, it describes the effect of tolvaptan as the first disease-modifying drug on kidney pain incidence, another important part of the ADPKD phenotype besides TKV growth and eGFR loss.

In conclusion, this study shows that a history of urinary tract infection, kidney stones, or hematuria and female sex were associated with a history of kidney pain at baseline, as well as with incident kidney pain events during the trial. No association was found between TKV and history of pain at baseline or with incident kidney pain events during the trial, indicating that kidney volume per se did not play a major role in causing pain. Tolvaptan use was

associated with a lower incidence of acute kidney pain events in all subgroups defined according to pain severity and independent of factors predisposing to pain incidence. The tolvaptan-induced reduction in incidence of renal complications, such as urinary tract infections, kidney stones, and hematuria, may at least in part explain the kidney pain-lowering effect of this drug.

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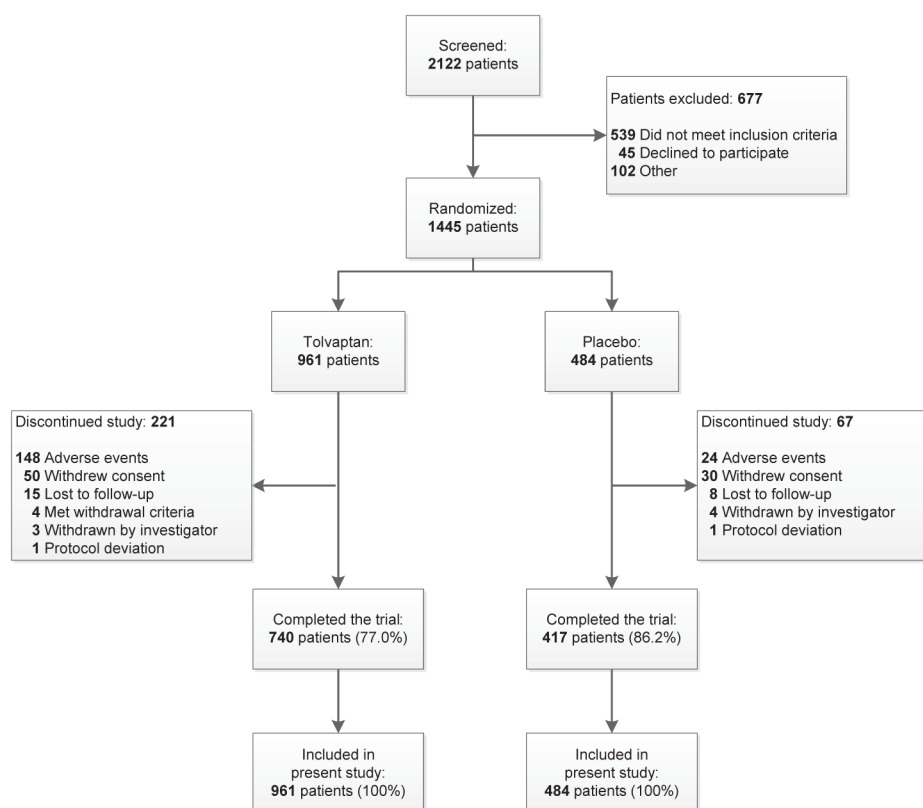
*Contributions:* Research area and study design: JDB, ABC, FSC, OD, EH, JO, RDP, VET, RTG; data acquisition: NFC, JDB, FSC, JO, RTG; data analysis/interpretation: NFC, JDB, JO, RTG; statistical analysis: NFC, JDB, JO, RTG; supervision or mentorship: ABC, OD, EH, AML, RDP, VET, RTG. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. RTG takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

*Peer Review:* Evaluated by 2 external peer reviewers, a Statistical Editor, and an Acting Editor-in-Chief.

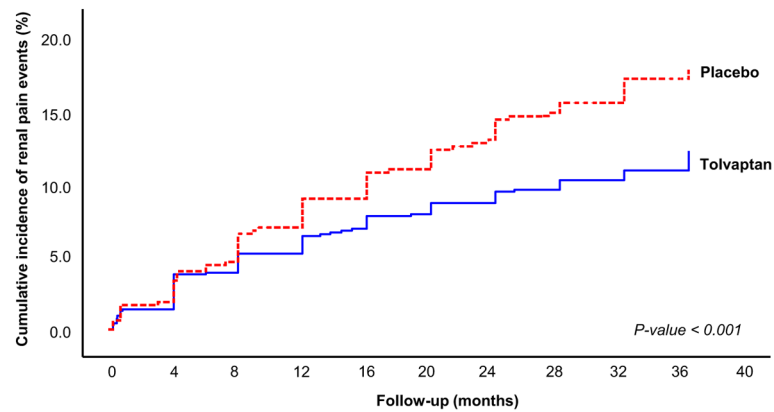
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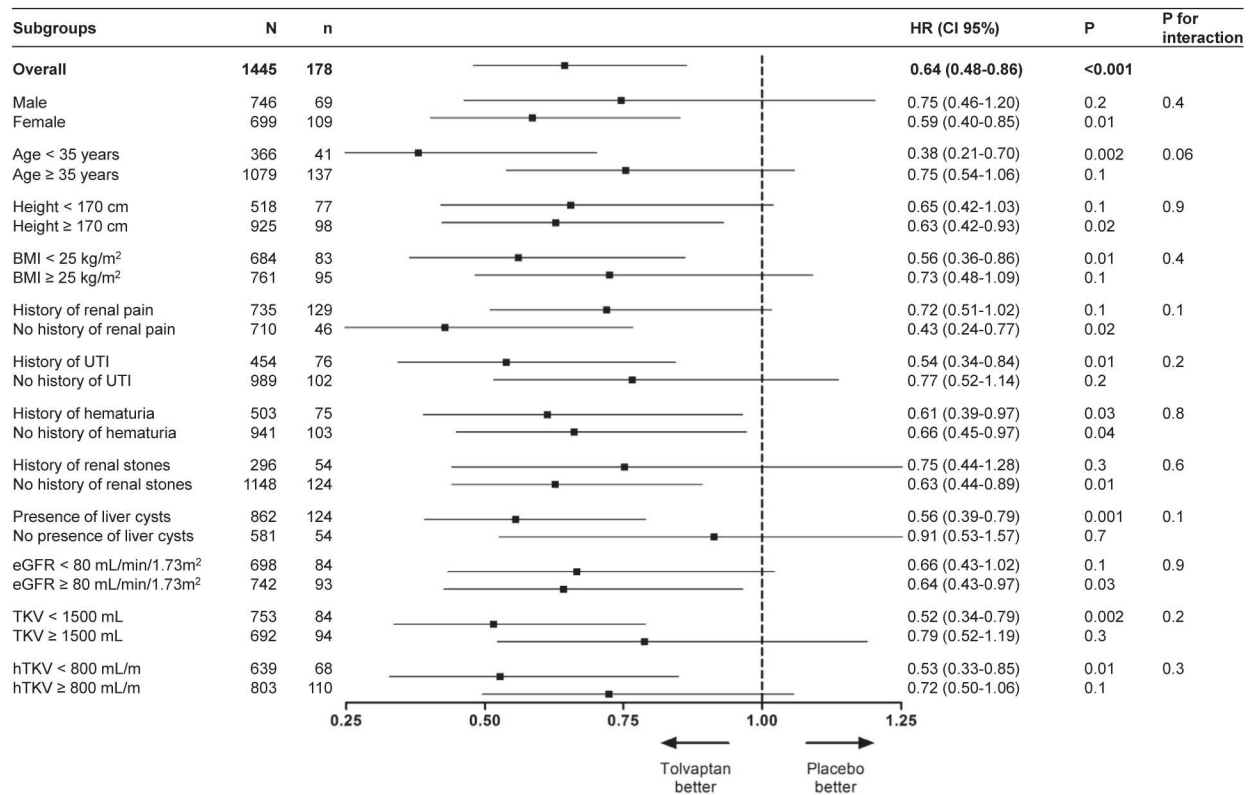


**Figure 1.**  
Patient enrollment and outcomes.



**Figure 2.**

Cumulative incidence of patients having a first kidney pain event in tolvaptan- (blue solid line,  $n = 97$ ) and placebo- (red dashed line,  $n = 81$ ) treated patients from baseline to month 36. Tolvaptan use was associated with a significantly lower incidence of first kidney pain events when compared to placebo, with a risk reduction of 36% (hazard ratio [HR], 0.64; 95% confidence interval, 0.48–0.86;  $P < 0.001$ ). Assessment of the assumption of proportional hazards indicated that the HR was constant over time (Figure S1).

**Figure 3.**

Effect of tolvaptan on first acute kidney pain events versus placebo during 3 years' follow-up in the overall study population and in subgroups according to baseline characteristics. Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; HR, hazard ratio; hTKV, height-adjusted total kidney volume; N, number of participants; n, number of events; TKV, total kidney volume; UTI, urinary tract infection.



**Table 1**

Baseline Characteristics of TEMPO 3:4 Trial Participants Stratified According to History of Kidney Pain

|                                  | <b>History of Kidney Pain</b> |                     | <b>P</b> |
|----------------------------------|-------------------------------|---------------------|----------|
|                                  | <b>Yes (n = 735)</b>          | <b>No (n = 710)</b> |          |
| Female sex                       | 389 (52.9)                    | 310 (43.7)          | <0.001   |
| Age, y                           | 38.8 ± 7.0                    | 38.4 ± 7.2          | 0.2      |
| Height, cm                       | 172.9 ± 10.1                  | 174.2 ± 10.1        | 0.01     |
| Weight, kg                       | 79.3 ± 18.4                   | 79.0 ± 18.1         | 0.9      |
| BMI, kg/m <sup>2</sup>           | 26.4 ± 5.3                    | 25.9 ± 4.8          | 0.2      |
| History of                       |                               |                     |          |
| UTI                              | 307 (41.9)                    | 147 (20.7)          | <0.001   |
| Hematuria                        | 318 (43.3)                    | 185 (26.1)          | <0.001   |
| Kidney stones                    | 196 (26.7)                    | 100 (14.1)          | <0.001   |
| Liver cysts                      | 450 (61.4)                    | 412 (58.0)          | 0.2      |
| Systolic BP, mm Hg               | 128.6 ± 13.3                  | 128.5 ± 13.7        | 0.9      |
| Diastolic BP, mm Hg              | 82.6 ± 9.5                    | 82.4 ± 10.0         | 0.9      |
| Use of BP-lowering drug          | 529 (72.0)                    | 510 (71.8)          | 0.9      |
| Presence of hypertension         | 609 (82.9)                    | 583 (82.1)          | 0.7      |
| eGFR, mL/min/1.73 m <sup>2</sup> | 82.4 ± 21.8                   | 80.8 ± 21.4         | 0.2      |
| TKV, mL                          | 1,694 ± 899                   | 1,690 ± 912         | 0.7      |
| hTKV, mL/m                       | 976 ± 501                     | 967 ± 508           | 0.5      |
| Urine osmolality, mOsm/kg        | 493.4 ± 175.5                 | 510.4 ± 181.8       | 0.04     |
| ACR, mg/mmol                     | 3.1 [1.2–8.1]                 | 3.3 [1.1–8.8]       | 0.2      |

*Note:* Values for categorical variables are given as number (percentage); values for continuous variables, as mean ± standard deviation or median [interquartile range].

Abbreviations: ACR, albumin-creatinine ratio; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; hTKV, height-adjusted total kidney volume; TEMPO, Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; TKV, total kidney volume; UTI, urinary tract infection.

**Table 2**

Associations of Baseline Characteristics With First Kidney Pain Events During 3 Years' Follow-up in the 484 Placebo-Treated Patients in TEMPO 3:4 Trial

|                                                | Crude            |        | Adjusted for Age, Sex, hTKV, eGFR |       |
|------------------------------------------------|------------------|--------|-----------------------------------|-------|
|                                                | HR (95% CI)      | P      | HR (95% CI)                       | P     |
| Female sex                                     | 2.01 (1.27–3.20) | 0.003  | 2.15 (1.33–3.45)                  | 0.002 |
| Age, per 5 y older                             | 0.97 (0.83–1.13) | 0.7    | 0.99 (0.83–1.18)                  | 0.9   |
| Height, per 5 cm greater                       | 0.85 (0.75–0.96) | 0.01   | 0.92 (0.78–1.09)                  | 0.3   |
| Weight, per 5 kg greater                       | 0.95 (0.89–1.02) | 0.1    | 0.98 (0.91–1.06)                  | 0.6   |
| BMI, per 1 kg/m <sup>2</sup> greater           | 1.00 (0.95–1.04) | 0.8    | 1.00 (0.95–1.05)                  | 0.9   |
| History of                                     |                  |        |                                   |       |
| Kidney pain                                    | 2.24 (1.40–3.58) | <0.001 | 2.15 (1.33–3.48)                  | 0.002 |
| UTI                                            | 2.00 (1.28–3.12) | 0.002  | 1.54 (0.94–2.51)                  | 0.08  |
| Hematuria                                      | 1.55 (0.99–2.43) | 0.1    | 1.75 (1.10–2.79)                  | 0.01  |
| Kidney stones                                  | 1.63 (1.01–2.64) | 0.04   | 1.84 (1.13–3.00)                  | 0.01  |
| Systolic BP, per 5 mm Hg greater               | 1.00 (0.92–1.09) | 0.9    | 1.03 (0.95–1.12)                  | 0.5   |
| Diastolic BP, per 5 mm Hg greater              | 1.08 (0.95–1.21) | 0.2    | 1.12 (0.99–1.26)                  | 0.1   |
| Use of BP-lowering drug                        | 0.88 (0.54–1.44) | 0.6    | 0.93 (0.55–1.58)                  | 0.8   |
| Presence of hypertension                       | 1.20 (0.63–2.27) | 0.6    | 1.36 (0.69–2.69)                  | 0.4   |
| eGFR, per 5 mL/min/1.73 m <sup>2</sup> greater | 1.00 (0.96–1.06) | 0.8    | 1.00 (0.94–1.06)                  | 0.9   |
| Log TKV, per doubling of TKV in mL             | 0.96 (0.67–1.37) | 0.8    | 0.14 (0.76–1.73)                  | 0.3   |
| Log hTKV, per doubling of hTKV in mL/m         | 1.02 (0.71–1.45) | 0.9    | 1.17 (0.77–1.75)                  | 0.5   |
| Urine osmolality, per 50 mOsm/kg greater       | 0.98 (0.92–1.04) | 0.4    | 0.98 (0.92–1.04)                  | 0.5   |
| Log ACR, per doubling of ACR in mg/mmol        | 1.09 (0.95–1.25) | 0.2    | 1.08 (0.93–1.26)                  | 0.3   |

*Note:* In multivariate analyses, risks were adjusted for age, sex, hTKV, and eGFR. In case the association between eGFR and first acute kidney pain event was investigated, the variable eGFR was not incorporated twice in the model.

Abbreviations: ACR, albumin-creatinine ratio; BMI, body mass index; BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; hTKV, height-adjusted total kidney volume; TEMPO, Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes; TKV, total kidney volume; UTI, urinary tract infection.

**Table 3**

Cumulative Incidence of Patients Having a Kidney Pain Event During 3 Years' Follow-up According to Severity of Pain as Scored by Intensity of Intervention

| Pain Severity              | Pain Events/100 person-y F/U | HR (95% CI)      | NNT | P      |
|----------------------------|------------------------------|------------------|-----|--------|
| Mild or worse (overall)    |                              |                  |     |        |
| Tolvaptan                  | 5.09                         | 0.64 (0.48–0.86) | 35  | <0.001 |
| Placebo                    | 8.09                         |                  |     |        |
| Moderate or worse          |                              |                  |     |        |
| Tolvaptan                  | 4.05                         | 0.62 (0.45–0.86) | 39  | 0.01   |
| Placebo                    | 6.74                         |                  |     |        |
| Moderately severe or worse |                              |                  |     |        |
| Tolvaptan                  | 2.94                         | 0.67 (0.45–1.00) | 64  | 0.05   |
| Placebo                    | 4.55                         |                  |     |        |
| Severe or worse            |                              |                  |     |        |
| Tolvaptan                  | 2.31                         | 0.74 (0.46–1.18) | 94  | 0.2    |
| Placebo                    | 3.40                         |                  |     |        |
| Most severe                |                              |                  |     |        |
| Tolvaptan                  | 0.21                         | 0.22 (0.04–1.14) | 384 | 0.07   |
| Placebo                    | 0.38                         |                  |     |        |

Abbreviations and Definitions; CI, confidence interval; F/U, follow-up; HR, hazard ratio; mild, prescription of acetaminophen; moderate, prescription of non-narcotic analgesics; moderately severe, limitation in physical activity; most severe, need for hospitalization and/or invasive intervention; NNT, number needed to treat; severe, prescription of narcotic analgesics.

**Table 4**

Change in TKV, Kidney Function, and Cumulative Incidence of Renal Complications Known to be Associated With Acute Pain in Placebo and Tolvaptan Groups During 3 Years' Follow-up

|                                                  | Placebo    |            |            |        | Tolvaptan  |            |            |        |
|--------------------------------------------------|------------|------------|------------|--------|------------|------------|------------|--------|
|                                                  | Overall    | Pain       | No Pain    | P      | Overall    | Pain       | No Pain    | P      |
| No. of patients                                  | 484        | 81         | 403        |        | 961        | 97         | 864        |        |
| Change in TKV, % per y                           | 5.6 ± 5.3  | 6.5 ± 6.9  | 5.4 ± 4.9  | 0.2    | 2.8 ± 5.7  | 2.8 ± 5.0  | 2.8 ± 5.7  | 0.9    |
| Change in eGFR, mL/min/1.73 m <sup>2</sup> per y | -3.7 ± 5.8 | -3.8 ± 4.8 | -3.7 ± 5.9 | 0.4    | -2.3 ± 8.7 | -3.1 ± 7.9 | -2.2 ± 8.8 | 0.02   |
| Incidence of                                     |            |            |            |        |            |            |            |        |
| UTI                                              | 15.3       | 24.7       | 13.4       | 0.02   | 11.1       | 16.5       | 10.5       | 0.1    |
| Hematuria                                        | 14.3       | 32.1       | 10.7       | <0.001 | 8.0        | 21.7       | 6.5        | <0.001 |
| Kidney stones                                    | 3.5        | 12.4       | 1.7        | <0.001 | 2.2        | 9.3        | 1.4        | <0.001 |
| Any of the above                                 | 28.7       | 51.2       | 24.1       | <0.001 | 18.9       | 41.2       | 16.4       | <0.001 |

*Note:* Data are given overall and separately for patients having and not having kidney pain events. Unless otherwise indicated, values for categorical variables are given as percentage; values for continuous variables, as mean ± standard deviation.

Abbreviations: eGFR, estimated glomerular filtration rate; TKV, total kidney volume; UTI, urinary tract infection.